REMARKS / ARGUMENTS

The Examiner has maintained her rejections of pending claims 1-16 based on two different combinations of references, both containing the primary reference, van Reis. A closer look at both the van Reis reference and Applicant's invention will show that the Examiner's rejections are without basis and cannot stand.

Rejections Maintained

Claims 1-16 remain rejected as allegedly being obvious over the combination of van Reis et al. (*Biotechnology and Bioengineering, Vol. 38, p. 413-422, 1991)* and U.S. Patent No. 5,780,601 granted to Green et al.

Claims 1-16 also remain rejected as allegedly being obvious over the van Reis article in view of Anilionis et al. (*U.S. Patent No. 5,098,997*) and further in view of Kolbe (*U.S. Patent No. 5,276,141*).

Common to both of these rejections is the Examiner's reliance on the primary reference, van Reis et al.. The Examiner contends that the van Reis reference combined with the Green reference and the Anilionis/Kolbe references make the use of tangential flow filtration (TFF) for purification of Protein e (P4) obvious to one skilled in the art, and therefore, not patentable. This contention combines differential detergent extraction as taught by Green and Anilionis with TFF as taught by van Reis. While each of these techniques by themselves is not novel, the Examiner's use of them together constitutes an egregious error. The key point of her contention is that one skilled in the art would be motivated by the van Reis reference to apply TFF to differential detergent extraction. The Examiner ignores the main points of the van Reis reference, which clearly states: "An industrial-scale method for harvest of biologically active proteins from mammalian cell cultures has been developed using tangential flow filtration". The Examiner even reiterates in her rejections the advantages of TFF cited within the article, namely the benefit of low sheer processing, cell containment, high yields, etc.

It is Applicant's position that each reference must be examined in its entirety if it is to be combined with another reference to allegedly defeat the patentability of the claimed invention. Even the Federal Circuit looks at each reference individually, as well as the prior art as a whole, for the suggestion to combine the references in a manner that renders the claimed invention obvious. *See Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5

USPQ2d 1434, 1438-39 (Fed. Cir. 1988) ("There is no suggestion in any individual prior art reference of such a combination of location and configuration nor is it suggested by the prior art as a whole.")

The van Reis reference is directed to methodologies that specifically allow the mammalian cells to remain intact and not be lysed. Lysing of the cells is stated as a common problem in other purification techniques, "High sheer stress can cause cell rupture resulting in increased levels of contaminating proteins and nucleic acids. In addition, added cell debris will reduce the capacity of downstream sterile filters." (Page 413, col. 2) The whole purpose of using TFF within the van Reis reference is to minimize sheer stress and hence reduce or eliminate lysis of the mammalian cells.

In contrast, the instant invention utilizes TFF in a process in which the first step is lysis of bacterial cells, combined with differential detergent extraction of membrane proteins. This initial lysis will release nucleic acids and contaminating proteins, situations that van Reis clearly states are undesirable and TFF is able to avoid, thus making it unlikely that one skilled in the art would be taught by van Reis to try TFF for process purification of the membrane proteins. Furthermore, one skilled in the art would know that differential detergent extraction is performed at or above the critical micelle concentration (CMC) of the detergent, assuring that the detergent and extracted membrane proteins will mostly be in micelles. The unobviousness of the claimed invention is the ability to use TFF with all of these factors that one skilled in the art would have thought should mitigate its use, as taught by van Reis. The van Reis reference presents the use of TFF as a method highly suited to situations where one does not wish to lyse mammalian cells, due to its uniquely low sheer stress. Neither the van Reis reference nor any of the secondary references makes mention of any of the factors that the inventors overcame in their successful use of TFF, including how to ascertain that one could move detergent micelles through a tangential flow filter without clogging, how to choose filters for such a use, how to change detergents, what criteria are used to judge such parameters, etc. It is these inventive steps that distinguish the claimed invention. The van Reis reference at best serves as a possible methodology for evaluation, but one that teaches away from its use in the situation faced by the inventors of the presently claimed invention.

The use of differential detergent extraction (Green et al. and Anilionis et al.) to purify the protein is not novel, but it is precisely its combination with TFF that makes the

claimed invention novel and unobvious. Thus, the van Reis reference and its inherent teaching that keeping the cells intact is a benefit of TFF, and by implication, that use of TFF would be of little value if the cells were lysed, steers one away from applying TFF to a process for extracting integral membrane proteins as recited in the claimed invention. Indeed, the Federal Circuit has repeatedly recognized that proceeding contrary to the accepted wisdom in the art represents "strong evidence of non-obviousness." *In re Hedges*, 228 USPQ 685, 687 (Fed. Cir. 1986); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 220 USPQ 303, 312 (Fed. Cir. 1983), *cert denied*, 469 U.S. 851 (1984).

Since the van Reis reference teaches away from the claimed invention, its combination with any of the secondary references cannot support the Examiner's rejections.

In view of the above remarks, Applicants submit that the present application is in condition for allowance, and a Notice to that effect is requested.

Respectfully submitted,

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